

distinctly claim the subject matter which applicant regards as the invention. Independent claims 35 and 42 have been amended as suggested by the Examiner. The amendment obviates this rejection.

II. Rejection under 35 U.S.C. §103, as being unpatentable over the prior art. Claims 35-51 have been rejected under 35 U.S.C. §103, as being unpatentable over Bachovchin (*J. Biol. Chem.* 265:3738-3743, 1990) or Bachovchin *et al.* (U.S. Patent 4,935,493) or Bachovchin *et al.* (WO 89/03223) or Flentke (*Proc. Natl. Acad. Sci. USA* 88:1556, 1991).

The Examiner cites a single statement in the *J. Biol. Chem.* Bachovchin reference (Bachovchin JBC) as grounds for rejecting the pending claims. Specifically, the Examiner takes the position that the statement "the early fraction appears, from the NMR spectra, to be approximately 95% enriched in one isomer" represents the description of a composition containing 95% of one isomer of a relevant compound.

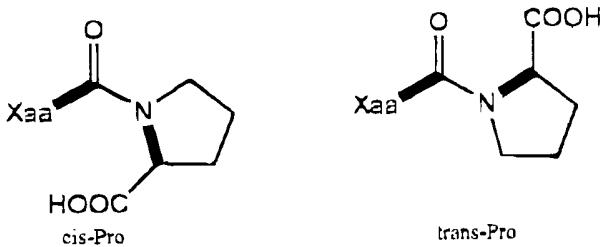
Applicant has previously pointed out that the statement made in Bachovchin JBC and relied upon by the Examiner *was an incorrect statement*, as has since been demonstrated in the literature and in declaratory evidence submitted to the Patent and Trademark Office (a copy of the previously submitted Declaration is enclosed with the present Response). The procedures followed in the Bachovchin JBC reference *did not*, and *can not*, produce a composition comprising 95% of one isomer of the compound. Thus, as Applicant has previously argued, the Bachovchin JBC reference does not teach one of ordinary skill in the art to produce a composition comprising 95% of one isomer, does not in fact describe such a composition, and therefore is not an enabling reference against the present claims. Applicant strongly reasserts this view.

In the Advisory Action mailed February 1, 2000, the Examiner has rejected Applicant's previous arguments with rationale that suggests a misunderstanding or misapplication of the law and the facts regarding the claimed invention. Specifically, the Examiner states "if a chemist stumbles onto the truth fortuitously, and reports in a publication that he obtained compound "X", such a report can be sufficient to bar a later scientist from being granted a monopoly on compound "X", even if the level of sophistication of the experiments carried out by the later

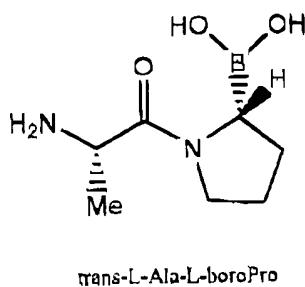
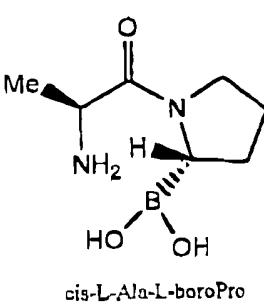
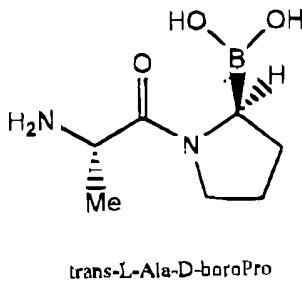
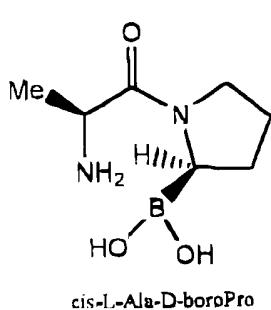
Bachovchin JBC did not stumble on the claimed composition; the authors did misidentify the resulting compounds as the ones claimed. The Examiner's position appears to be an inherency rejection—that the presently claimed invention is inherent in what Bachovchin JBC discloses. However, a proper inherency rejection requires that the reference be enabling and be reproducible. As is stated in *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1983), "the mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference." As amply described in the Declaration of April 1, 1999 and reiterated and amplified in the Declaration filed with this Response and discussed below, performing steps of Bachovchin JBC does not produce the stated result (*i.e.*, a composition containing 95% of one isomer).

The Examiner has previously challenged the assertions presented in the Bachovchin Declaration of April 1, 1999, but a careful analysis of the Examiner's comments reveals that they reflect a misunderstanding of the relevant technology. Specifically, in the Final Office Action mailed June 24, 1999, the Examiner offered a variety of technological reasons to reject the statements made in the April 1, 1999 Bachovchin Declaration. Many of the assertions made by the Examiner are scientifically inaccurate. Specific assertions are addressed individually below; a Table is also provided that summarizes Applicant's rebuttal of each of the Examiner's statements. A second Bachovchin Declaration is also provided, to support Applicant's rebuttal statements.

By way of background, Applicant first points out that, due to the partial double-bond character of the C-N linkage in an amide bond, certain amino acids, including proline, can exist in either a *cis* or a *trans* conformation with respect to the amide bond:

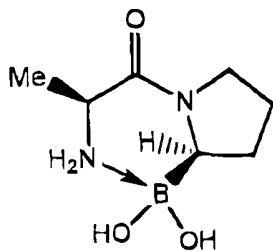


trans conformation is independent of and unrelated to the stereochemistry at the alpha carbon. Therefore, four possible isomers of the compounds disclosed in Bachovshin JBC exist: the *trans*-L,L-isomer, the *trans*-L,D-isomer, the *cis*-L,L-isomer, and the *cis*-L,D-isomer. These four isomers are shown below:



As was stated in paragraph 7 of the Declaration filed April 2, 1999, Xaa-boroPro molecules undergo an equilibration between the *cis* and *trans* conformation. NMR data supporting this hypothesis was provided in paragraphs 8-12 of the same Declaration and has been published in several scientific papers (Gunther *et al.* "Solution Structures of the DP IV (CD26) Inhibitor Val-boroPro Determined by NMR Spectroscopy" *Magnetic Resonance in Chemistry* 33:959-970, 1995; Sudmeier *et al.* "Solution Structures of Active and Inactive Forms of the DP IV (CD26) Inhibitor Pro-boroPro Determined by NMR Spectroscopy" *Biochemistry* 33:12427-12438, 1994; Snow *et al.* "Studies on Proline Boronic Acid Dipeptide Inhibitors of Dipeptidyl Peptidase IV: Identification of a Cyclic Species Containing a B-N Bond" *J. Am. Chem. Soc.* 116:10860-10869, 1994; Kelly *et al.* "Immunosuppressive Boronic Acid Dipeptides: Synthesis and Structure-Activity Relationship" *J. Am. Chem. Soc.* 115:12627-12638, 1993).

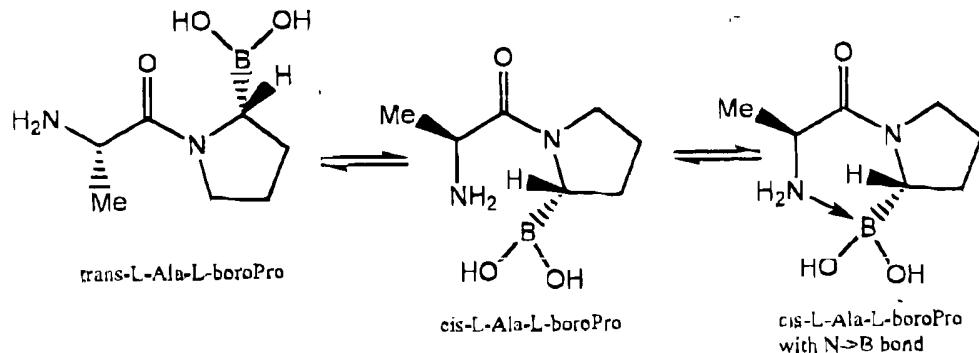
copy of each of these references has been submitted with the IDS for this application and an additional copy has been enclosed herewith). In addition, the *cis* isomer due to the geometry of the boron of proline and the nitrogen of alanine can form a covalent N->B bond (shown below). The *trans* isomer does not undergo this cyclization (*i.e.*, no N->B bond forms) due to the geometry of the nitrogen and boron (*i.e.*, they are not close enough together in the *trans* conformation to form a covalent bond), as stated in paragraphs 6 and 12 of the Declaration filed with this Response.



As stated previously in paragraph 13 of the Declaration filed April 2, 1999, the early and later fractions described in Bachovchin JBC do *not* represent the L,L and L,D isomers *but rather* the *cis* and *trans* isomers. More specifically, the early fraction represents the *trans* isomers, both L,L and L,D; and the later fraction represents the *cis* isomers, both L,L and L,D (see paragraphs 8 and 9 of the Declaration submitted April 2, 1999). The separation effected by silica gel chromatography as described in Bachovchin JBC is based entirely on the *cis/trans* geometry of the amide bond. There was *no* separation based on the stereochemistry of the alpha-carbon of boroProline; therefore, the L,L and L,D isomers were not separated. The Examiner has proposed separating the L,L and L,D stereoisomers by repeatedly passing the mixture through a silica gel column; however, even multiple passes of the mixture of isomers over a silica gel column would not yield separation of the L,L and L,D isomers (see paragraph 14 of the Declaration submitted with this Response).

One of the reasons given by the Examiner for rejecting the April 1, 1999 Bachovchin Declaration is that "there is a contradiction" in the Declaration because it discusses both a conformation equilibrium and a covalent bond (see Final Office Action of June 24, 1999, page 3, starting on line 1). This statement by the Examiner represents a misunderstanding of the science. There is no contradiction in the Declaration. The "conformation equilibrium on . . . a slow time

of a bond between nitrogen and boron. A molecule in the *cis* conformation may subsequently undergo cyclization with the formation of a nitrogen to boron bond. However, this N->B covalent bond is labile allowing for the N->B bond to break and the *cis* isomer to convert back to the *trans* isomer as shown in the scheme below. As stated above and in paragraph 6 of the Declaration submitted herewith, the *trans* isomer does not form a cyclic structure.



The April 1, 1999 Bachovchin Declaration includes a statement that the results observed in the Bachovchin JBC reference might be explained by co-elution on a silica gel column of the *cis*-L,D and the *cis*-L,L isomers with one another, and the separate co-elution of the *trans*-L,D and *trans*-L,L isomers. In the June 24, 1999 Final Office Action, the Examiner rejects this conclusion by offering three arguments that are each scientifically flawed.

First, the Examiner offers that the Declaration also asserts the existence of a conformational equilibrium rather than a covalent bond. As discussed above, the conformational equilibrium refers to an equilibrium between the *cis* and *trans* conformations, and is not relevant to the existence of a covalent bond. The fact is that the interconversion of the *cis* and *trans* isomers is on such a slow time scale that the two isomers are separable by silica gel chromatography. There need be no covalent bond in order to effect separation of the two isomers.

Second, the Examiner asserts that "the *trans*-isomer would not be 'trapped' by the boron atom." This is correct. However, the Examiner goes on to assert that there would be no *cis/trans* isomerization for compounds in which no covalent bonding was present. This is incorrect.

formed. *Cis/trans isomerization does not rely on the formation of a covalent bond.*

Third, the Examiner questions the identity of the "bone-fide" L,L-isomer, particularly whether it is in the *cis* or *trans* conformation and whether a covalent bond between the boron and nitrogen is present. The NMR spectrum of the "bone-fide" L,L-isomer, presented as exhibit C in the previously filed Declaration, is the spectrum of the *trans*-L,L-isomer, with no covalent bond present. The Applicant apologizes for not more clearly identifying the structure to which the spectrum pertains and regrets any confusion this may have caused..

Yet another reason given by the Examiner for rejecting the statements of the April 1, 1999 Bachovchin Declaration is that the Examiner simply doubts the existence of a cyclic *trans* isomer (see Final Office Action of June 24, 1999, page 4, line 5-6). The Examiner is correct in that the *trans* isomer does not form a cyclic structure. However, the *cis* isomer does. NMR data provided with the April 1, 1999 Bachovchin Declaration supports the existence of a cyclic *cis* isomer; if those data, in combination with the present Response are insufficient to convince the Examiner of Applicant's position, Applicant respectfully requests that the Examiner provide more specific reasons for challenging the data evidencing existence of the structure.

A final reason given by the Examiner for finding the Bachovchin Declaration and related arguments unpersuasive is that the Examiner asserts that a second pass of the mixture described in the Bachovchin JBC reference through silica gel would provide higher purity, as recited in the present claims (*e.g.*, greater than 95% purity). Once again, this statement reveals the Examiner's misunderstanding of the science. Silica gel chromatography separates *cis* isomers from *trans* isomers, but does not separate L,L isomers from L,D isomers. Thus, no number of passages through silica gel could result in a composition with the claimed isomeric purity.

For all of these reasons, Applicant submits that the Examiner has inappropriately rejected the statements and assertions made in the April 1, 1999 Bachovchin Declaration. That Declaration, in combination with arguments made both in the December 22, 1999 Response to Final Office Action and herein, amply demonstrate that the Bachovchin JBC reference is not enabling; performance of the steps recited in that reference *does not* produce the claimed compositions.

Furthermore, the Examiner's maintenance of the claim rejection over the Bachovchin

the second example presented in the Advisory Action of February 1, 2000. The Examiner states "if chemist published a structure of compound "X", and it turned out that the structure he had determined was not correct, a later chemist would be barred from claiming the published structure for a compound "Y", even if the later chemist were entirely correct in his structure determination." This is not the law. As is clearly stated in *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1983):

The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference.

If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be. In view of the fact that the purpose sought to be effectuated by the patent law is the encouragement of innovation, such a result would be repugnant to the statute.

(See also *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)).

The Examiner also apparently misunderstands the facts of the present case. In the Advisory Action of February 1, 2000, the Examiner sets out a "third example" (beginning on page 2 at line 15), which the Examiner characterizes as "closer to the case at hand" than the second example discussed above. The Examiner says "if a first chemist publishes a structure of compound "X", and he later turns out to be absolutely correct, a second chemist would not be granted a patent claim for the structure of compound "X" merely because the first chemist had admitted that he was not absolutely certain of the structure." The issue in the present case is *not* that the authors of Bachovchin JBC were uncertain that they had achieved 95% optical purity, but rather that they did not in fact achieve such purity. Thus, the present situation is closer to Example 2 and not Example 3.

In light of the evidence presented and arguments made herein, Applicant respectfully requests that the rejection over the Bachovchin JBC reference be removed.

This leaves only U.S. Patent 4,935,493 by Bachovchin *et al.*, the publication of the

Sci. USA 88:1556-1559, February 1991). As has already been established, these publications do not teach or suggest a mixture of isomers at least 96% enriched for molecules of the L-configuration at the carbon atom bearing boron, as recited in the present claims. In fact, the Examiner acknowledges that the '493 patent does not form the basis for a proper §102 rejection. And the Examiner has not challenged the assertion by the Applicant that it would not have been obvious to switch from silica gel to a C18 matrix to purify the desired compound. The remaining legal question, then, is whether the disclosure of these references would both (i) motivate a-chemist of ordinary skill to try to prepare a composition comprising at least 96% of one isomer; and (ii) provide sufficient guidance for the preparation of such a composition that a chemist would have a reasonable expectation of success. Quite simply, these references do not contain any disclosure that would direct a chemist of ordinary skill to prepare a composition with at least 96% of the carbon atoms bearing boron being of the L-configuration. Moreover, even if the references were to suggest that it might be desirable to prepare such a composition, Applicant has previously pointed out that no method or strategy for obtaining such a composition is provided. The Examiner does not dispute that the '493 patent contains no description of method for preparing an isomerically biased composition. In light of this, these publications cannot render obvious the present claims.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

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Respectfully submitted,

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